ELEVATING THE STANDARD OF CARE FOR STIs: THE BD MAX™ CT/GC/TV ASSAY

AUTHORS: Diane Kawa, PhD; Brittany Kostiha; Judy H Yu, PhD; Megan LeJeune
BD Life Sciences - Diagnostic Systems

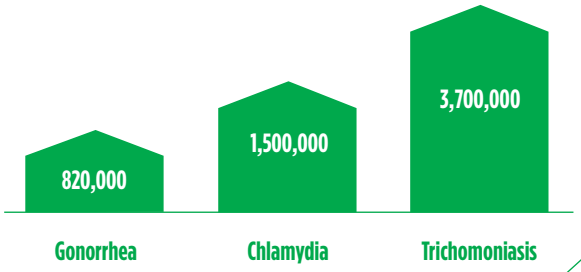
SUMMARY

In the United States, Chlamydia trachomatis (CT), *Neisseria gonorrhoeae* (GC), *and Trichomonas vaginalis* (TV) *are the most prevalent curable sexually transmitted infections (STIs) that can pose considerable health and economic burdens if left untreated. A single multiplex test that can effectively detect all 3 diseases in a single collection could increase efficiency of care across healthcare settings versus panels that cover chlamydia and gonorrhea alone. The BD MAX™ CT/GC/TV assay is an all-in-one automated DNA extraction and real-time polymerase chain reaction (PCR) test for the simultaneous detection of chlamydia, gonorrhea, and trichomoniasis from a single specimen collection. The overall sensitivity and specificity of the triplex BD MAX™ CT/GC/TV assay are 95.7% & 99.2% for CT, 97.1% & 99.9% for GC, and 94.1% & 99.2% for TV (females only), respectively, and the assay can accommodate urine, vaginal swab, or endocervical swab samples.*

INTRODUCTION

Chlamydia (CT), gonorrhea (GC), and trichomoniasis (TV) are among the most prevalent sexually transmitted infections (STIs) and pose a large and increasing public health burden.[1] Reports from the U.S. Centers for Disease Control and Prevention (CDC) estimate 1.5 million new chlamydial infections and 820,000 gonorrheal infections each year[2-4] **(Figure 1)**. TV, a much-neglected STI until recently, ranks third among all common STIs after HPV and chlamydia and has an estimated 3.7 million new and existing infections each year in the U.S. alone.[1] Globally, TV infection is responsible for approximately 50% of all curable STIs.[5]

FIGURE 1. ESTIMATED NUMBER OF NEW AND EXISTING (TOTAL) SEXUALLY TRANSMITTED INFECTIONS[3]



Although most of these infections are asymptomatic, if left unaddressed they can have serious consequences including pelvic inflammatory disease (PID), ectopic pregnancies, infertility, preterm or low-birth-weight infants, and increased risk of STI transmission or infection (including HIV) in males and females.[6-15] More specifically, CT can increase the risk for tubal factor infertility,[6] whereas both CT and TV have been associated with adverse reproductive health outcomes including PID,[8,10] late-term miscarriage, and low-birth-weight infants.[7,8,15] TV can also lead to increased HIV transmission.[8,9] In terms of co-infections, HIV-positive women are more likely, on average, to have TV. Moreover, if women test TV positive, there is increased susceptibility to HIV infection and higher HIV transmission rates, as well as an increased likelihood of syphilis.[12-14]

Targeted treatment based on the accurate diagnosis of CT, GC, or TV infection is necessary to improve patient quality of life and avoid sequelae. Increased diagnosis and treatment of TV could help to reduce this burden. In fact, treatment for TV can reduce HIV shedding and viral load in the genital tract and help lower the likelihood of HIV transmission.[16] Management of TV in HIV-positive women may help decrease the economic burden of both diseases, and can potentially do so in a more cost-effective manner than HIV antiretroviral therapy alone. For women between ages 15 and 24 years, the average total cost per patient is significantly higher than for women of other ages, at $120 per case of TV infection. The current economic burden is still not well understood due in part to limited testing.[17]

LIMITATIONS OF NON-MOLECULAR DIAGNOSTIC TECHNIQUES AND CDC RECOMMENDATIONS

Detection via clinical diagnosis alone for CT, GC, and TV is highly inaccurate. Many symptoms are similar across these 3 infections and TV is difficult to diagnose with conventional manual methods.[4,18,19] Screening for CT, GC, and TV is recommended for women who are symptomatic, HIV positive, or at high risk. Men should also undergo CT and GC screening if identified as high risk.[4]

In women, the same sexual behaviors that increase the risk of CT and GC also increase the risk of TV acquisition and transmission.[4] Consequently, current CDC guidelines recommend testing for CT and GC when the results of TV testing are positive.[4] Additionally, TV more commonly occurs in conjunction with CT than GC with CT,[20] which reinforces the desirability of testing these 3 infections simultaneously. Further, among women for whom CT screening is recommended, there is a higher disease burden of TV.[20-23] The strong evidence of co-infection and co-risk factors suggest the need to test for TV along with CT and GC.

THE BENEFITS OF MOLECULAR METHODS

A nucleic acid amplification test (NAAT) is the recommended standard of care for CT, GC, and TV testing because it is a highly sensitive and specific test.[24-26] Though many laboratories run CT/GC separately from trichomonas today, test options that can provide results for all 3 STIs are ideal in settings where the population is at increased risk.[23] Such a triplex test could increase efficiency through reduction of labor and detect more infections than panels that cover CT or GC alone.[24]

The BD MAX™ System is an automated in vitro diagnostic system for the direct, qualitative detection of infection/disease agents from a variety of patient specimens and is capable of performing 1 to 24 tests at a time. The BD MAX™ System offers an efficient path to improved laboratory efficiency through combining and automating real-time PCR extraction, amplification, and detection into a single platform.[27]

The BD MAX™ CT/GC/TV is a first-in-class triplex test that runs on the BD MAX™ System. It is an automated DNA extraction and real-time polymerase chain reaction (PCR) test for the simultaneous detection of CT, GC, and TV.[27] The BD MAX™ CT/GC/TV test has the potential to improve laboratory efficiency and patient management as an accurate, automated triplex assay that provides objective diagnosis for the 3 most prevalent non-viral STIs.

Clinicians and patients (in a clinical setting) can improve their clinical coverage of STI diagnostics without any incremental labor for TV by testing these 3 STIs with a triplex test. After just 1 run, results are provided as clear positives or negatives for all 3 infections. Concurrent testing of these 3 STIs may enhance patient management because it may reduce unnecessary costs and risks related to missed diagnosis and treatment of TV by providers, payers, and patients alike. Appropriate treatment often leads to reduced symptoms, resolved infections, and improved patient quality of life by mitigating the risk of sequelae such as STI transmission, PID, late-term miscarriage, and preterm birth. This test is just one of several offered on the BD MAX™ platform that enables clinical solutions for womens health and STI issues.

BD MAX™ CT/GC/TV ASSAY CHARACTERISTICS AND PERFORMANCE

A clinical trial was performed at 8 different clinical sites in North America to evaluate the sensitivity and specificity of the BD MAX™ CT/GC/TV assay **(Table 1)**. The assay's sensitivity and specificity values were determined by comparing assay reported outputs against the patient infected status (PIS) (see Methods). Assay performance for CT, GC, and TV was determined with the evaluation of a vaginal swab, an endocervical swab, and a urine specimen from female subjects and a urine specimen from men for evaluation of CT and GC.

For CT, the BD MAX™ CT/GC/TV assay demonstrated overall 99.3% sensitivity and 98.6% specificity using a vaginal swab, 98.5% sensitivity and 99.2% specificity using an endocervical swab, and 91.5% sensitivity and 99.5% specificity with a urine specimen. In male patients, the assay demonstrated 96.1% sensitivity and specificity of 99.4% using a urine specimen.

For GC, the overall assay performance was 95.5% sensitivity and 99.8% specificity using a vaginal swab, 97.7% sensitivity and 99.9% specificity using an endocervical swab, and 95.7% sensitivity and 99.7% specificity with a urine specimen. In males, the assay demonstrated 99.1% sensitivity and 100% specificity using a urine specimen.

For TV testing in female subjects, the assay demonstrated overall 96.1% sensitivity and 98.9% specificity using a vaginal swab, 93.4% sensitivity and 99.3% specificity using an endocervical swab, and 92.9% sensitivity and 99.3% specificity with a urine specimen.

Table 1 Overall Performance Compared with Patient Infected Status

Sex	Specimen	Status	*Chlamydia trachomatis*		*Neisseria gonorrhoeae*		*Trichomonas vaginalis*	
			Sens*	Spec**	Sens	Spec	Sens	Spec
Female	**Vaginal Swab**	Asymptomatic	**100%** (51/51) 93.0-100	**98.7%** (734/744) 97.5-99.3	**94.1%** (16/17) 73.0-99.0	**99.9%** (777/778) 99.3-100	**93.1%** (27/29) 78.0-98.1	**97.5%** (270/277) 94.9-98.8
		Symptomatic	**98.9%** (89/90) 94.0-99.8	**98.6%** (938/951) 97.7-99.2	**96.3%** (26/27) 81.7-99.3	**99.8%** (1012/1014) 99.3-99.9	**96.7%** (119/123) 91.9-98.7	**99.5%** (616/619) 98.6-99.8
		ALL	**99.3%** (140/141) 96.1-99.9	**98.6%** (1672/1695) 98.0-99.1	**95.5%** (42/44) 84.9-98.7	**99.8%** (1789/1792) 99.5-99.9	**96.1%** (146/152) 91.7-98.2	**98.9%** (886/896) 98.0-99.4
	Endocervical Swab	Asymptomatic	**98.0%** (48/49) 89.3-99.6	**99.1%** (739/746) 98.1-99.5	**100%** (16/16) 80.6-100	**100%** (778/778) 99.5-100	**96.6%** (28/29) 82.8-99.4	**98.2%** (270/275) 95.8-99.2
		Symptomatic	**98.8%** (84/85) 93.6-99.8	**99.4%** (945/951) 98.6-99.7	**96.3%** (26/27) 81.7-99.3	**99.9%** (1002/1003) 99.4-100	**92.7%** (114/123) 86.7-96.1	**99.8%** (611/612) 99.1-100
		ALL	**98.5%** (132/134) 94.7-99.6	**99.2%** (1684/1697) 98.7-99.6	**97.7%** (42/43) 87.9-99.6	**99.9%** (1780/1781) 99.7-100	**93.4%** (142/152) 88.3-96.4	**99.3%** (881/887) 98.5-99.7
	Urine	Asymptomatic	**92.3%** (48/52) 81.8-97.0	**99.7%** (747/749) 99.0-99.9	**88.9%** (16/18) 67.2-96.9	**99.5%** (779/783) 98.7-99.8	**93.1%** (27/29) 78.0-98.1	**98.2%** (272/277) 95.8-99.2
		Symptomatic	**91.1%** (82/90) 83.4-95.4	**99.4%** (952/958) 98.6-99.7	**100%** (28/28) 87.9-100	**99.9%** (1019/1020) 99.4-100	**92.8%** (116/125) 86.9-96.2	**99.8%** (615/616) 99.1-100
		ALL	**91.5%**[a] (130/142) 85.8-95.1	**99.5%** (1699/1707) 99.1-99.8	**95.7%**[b] (44/46) 85.5-98.8	**99.7%** (1798/1803) 99.4-99.9	**92.9%** (143/154) 87.7-96.0	**99.3%** (887/893) 98.5-99.7
Male	**Urine**	Asymptomatic	**98.6%** (69/70) 92.3-99.7	**99.5%** (378/380) 98.1-99.9	**80.0%** (4/5) 37.6-96.4	**100%** (447/447) 99.1-100		
		Symptomatic	**94.6%** (105/111) 88.7-97.5	**99.3%** (267/269) 97.3-99.8	**100%** (103/103) 96.4-100	**100%** (285/285) 98.7-100		
		ALL	**96.1%** (174/181) 92.2-98.1	**99.4%** (645/649) 98.4-99.8	**99.1%** (107/108) 94.9-99.8	**100%** (732/732) 99.5-100		

[a]Six of 12 CT false-negative urine specimens also tested negative by NAAT1 and NAAT 2 urine reference methods. [b]One of 2 GC false-negative urine specimens also tested negative by NAAT 1 and NAAT 2 urine reference methods.
*Sensitivity **Specificity

TABLE 2 Limit of Detection by the BD MAX CT/GC/TV

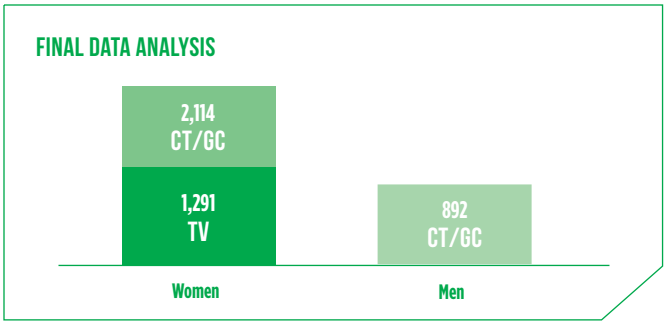
Table 2 summarizes the analytical sensitivity and limit of detection (LoD) of the BD MAX™ CT/GC/TV assay. The assay could detect 14 different serovars of CT in as few as 5 units per mL from urine and 9 units per mL from a vaginal swab. Thirty strains of GC were tested, and as few as 60 units per mL from urine or a vaginal swab were detected. Eight strains of TV were tested with the assay, and as few as 10 units per mL from a urine specimen and 5 units per mL from a vaginal swab were detected.

Organism	Strain	Specimen	LoD Concentration (units/mL)[a]
Chlamydia trachomatis	Serovar H	Urine	11
		Vaginal Swab	9
	Serovar D	Urine	5
		Vaginal Swab	13
Neisseria gonorrhoeae	ATCC 19424	Urine	60
		Vaginal Swab	60
	ATCC 49226	Urine	181
		Vaginal Swab	117
Trichomonas vaginalis	ATCC 30001	Urine	10
		Vaginal Swab	5
	ATCC 50143	Urine	34
		Vaginal Swab	10

[a]Units/mL LoD concentration represented in elementary bodies (EB)/mL for *Chlamydia trachomatis*, cells/mL for *Neisseria gonorrhoeae*, and TV/mL for *Trichomonas vaginalis*.

METHODS[27]

Eight geographically diverse clinical sites in North America participated in the clinical trial to evaluate the BD MAX™ CT/GC/TV assay.[27] The final data analysis included 2,114 evaluable female subjects for CT and GC, with 1,291 of these female subjects evaluable for TV. For males, 892 were evaluable subjects for CT and GC analyses.

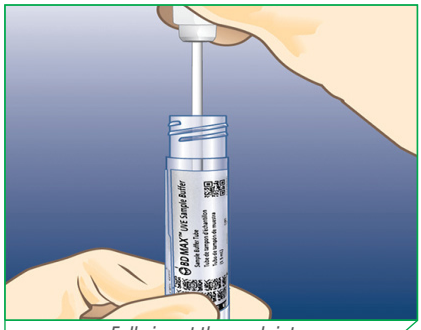


Eight specimens were collected from each eligible female subject. Urine was collected and aliquoted into the BD MAX UVE Sample Buffer Tube for testing on the BD MAX™ CT/GC/TV assay and the 2 reference urine specimen collection devices/tests. One patient-collected vaginal swab specimen was transferred into the BD MAX UVE Sample Buffer Tube **(Figure 1)** for testing on the BD MAX™ CT/GC/TV assay. Two randomized, clinician-collected vaginal swab specimens were collected for the *Trichomonas vaginalis* reference testing and 3 randomized endocervical swab specimens were collected for the BD MAX™ System and transferred to the BD MAX UVE Sample Buffer Tube for testing on the BD MAX™ CT/ GC/TV GC/TV assay and the 2 reference specimen collection devices/tests. Two specimens were collected from each of the eligible male subjects. Urine was aliquoted into the BD MAX UVE Sample Buffer Tube for testing on the BD MAX™ CT/GC/TV assay and the 2 reference specimen collection devices/tests. One urethral swab specimen was collected and tested using a reference method. Tests were performed on the BD MAX™ System according to BD MAX™ CT/GC/TV Assay workflow **(Figure 2)**.

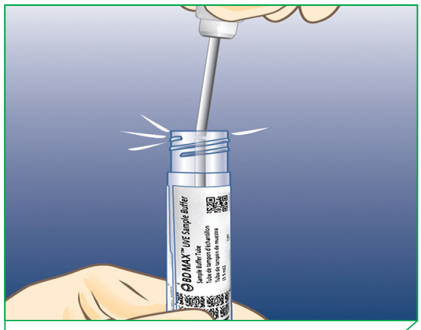
The performance of the BD MAX™ CT/GC/TV assay was calculated compared to patient infected status (PIS) (refer to **Table 1**). Comparative reference methods included 2 different commercially available NAATs for female subjects and 3 NAATs for male subjects from at least 2 different specimen types for CT and GC, and 2 tests (culture and wet mount) for TV. The subject was designated infected with CT and/or GC if at least 2 different reference NAATs were positive for urine and vaginal swabs. Endocervical infections occurred when the endocervical results were positive for both NAATs and the urine results were negative. For TV, the subject was designated infected if at least 1 of the reference results (wet mount or culture) was positive. Both TV reference results were required to be negative to establish non-infected status.

FIGURE 1

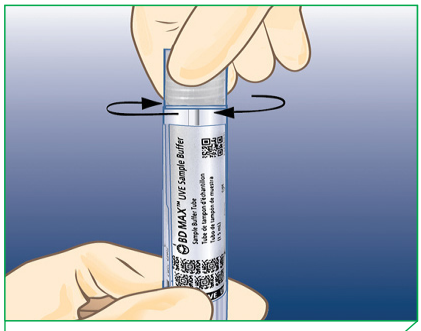
BD MAX™ CT/GC/TV Assay Sample Preparation



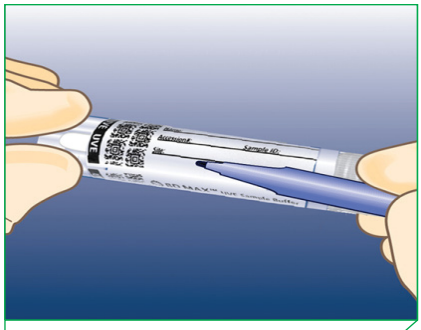
1 *Fully insert the swab into the tube so that the tip is at the bottom*



2 *Carefully break the shaft at the score mark*



3 *Tightly re-cap the tube*

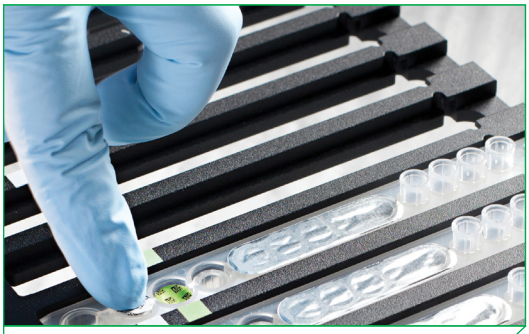


4 *Label tube with patient information*

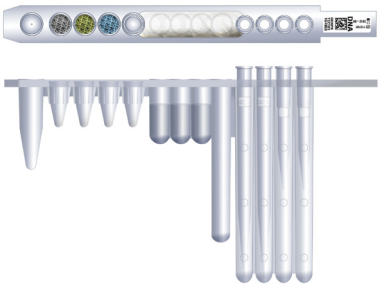
FIGURE 2

BD MAX™ CT/GC/TV Assay Workflow

(please refer to PI for workflow instructions)

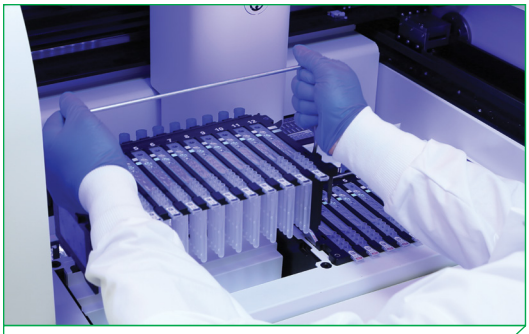


1 *Snap BD MAX CT/GC/TV Master Mix into Unitized Reagent Strips*



2 *Snap BD MAX CT/GC/TV Master Mix into Unitized Reagent Strips*

3 *Load PCR Cartridges*



4 *Load Rack(s) into the BD MAX™ System*

DISCUSSION

The BD MAX™ CT/GC/TV assay is an all-in-one extraction and amplification in vitro molecular diagnostic for the simultaneous detection of CT, GC, and TV. The panel delivers objective, clear positive and negative results for each target, and removes the interpretation and subjectivity inherent in wet-mount diagnostic methods for TV. This improved objectivity, combined with the sensitivity and specificity offered on the BD MAX™ System, can expand detection compared to CT/GC-only tests, particularly in cases of co-infection, and may help ensure that patients receive appropriate care for their STIs.

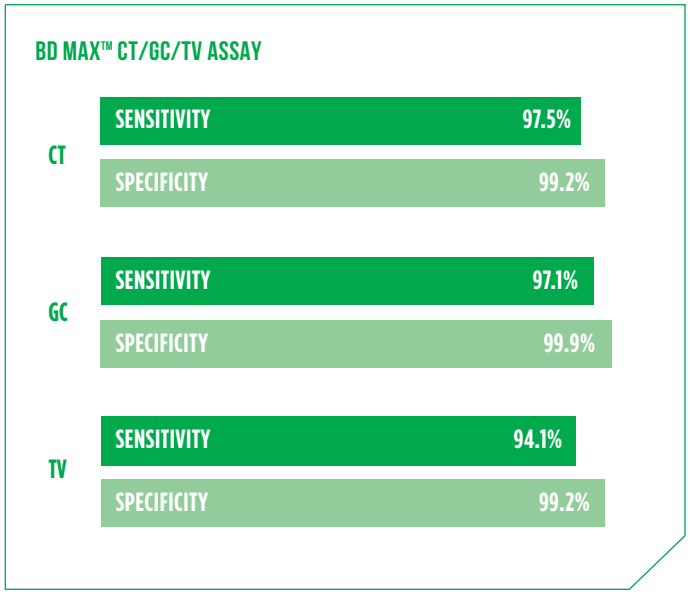
Several key characteristics of the assay that provide the foundation for this improved clinical coverage:

- The panel demonstrates 95.7% & 99.2% for CT, 97.1% & 99.9% for GC, and 94.1% & 99.2% for TV (females only) overall sensitivity and specificity for CT, GC, and TV, respectively, using a urine specimen, a vaginal swab, or an endocervical swab.[27]
- The panel identifies and reports CT, GC, and TV in one collection. In cases where co-infections are present, concurrent diagnosis of these 3 infections may improve treatment coverage.
- The panel uses NAAT for TV, which is more accurate than traditional methods and is the current recommended method.[4]
- The panel requires a single collection and test, which is simpler and more efficient than a combination of multiple manual tests. It also reduces the burden on clinicians and ensures better diagnostic coverage of patient symptoms.

Improving diagnostic coverage of the top 3 non-viral STIs has potential patient benefit. It may lead to better patient management by informing the appropriate choice of prescription medications for treatment and resolving more infection, especially for trichomoniasis. Treatment of these infections may in turn lead to reduced risk of sequelae such as pre-term birth, other STI transmission and acquisition including HIV, late-term miscarriage, and PID. For the provider and broader healthcare system, diagnosis of all 3 STIs in a single test can improve healthcare efficiency and relieve additional labor and collections.

CONCLUSION

The BD MAX™ CT/GC/TV assay performed with overall target sensitivity and specificity (respectively) of 95.7% & 99.2% for CT, 97.1% & 99.9% for GC, and 94.1% & 99.2% for TV (females only) using urine specimen from male subjects or urine specimen, a vaginal swab, or an endocervical swab from female subjects.



Advances in efficiency of testing such as those delivered by the BD MAX™ CT/GC/TV test may improve the diagnostic coverage of clinically prevalent STIs, which may lead to improved patient management.

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ADVANCES IN EFFICIENCY OF TESTING SUCH AS THOSE DELIVERED BY THE BD MAX™ CT/GC/TV TEST MAY IMPROVE THE DIAGNOSTIC COVERAGE OF CLINICALLY PREVALENT STIs, WHICH MAY LEAD TO IMPROVED PATIENT MANAGEMENT.

Talk to your BD representative about how you can enhance quality patient care with BD MAX CT/GC/TV.

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